12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes—2025

American Diabetes Association Professional Practice Committee*

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For prevention and management of diabetes complications in children and adolescents, please refer to Section 14, "Children and Adolescents."

DIABETIC RETINOPATHY

Recommendations

12.1 Implement strategies to help people with diabetes reach glycemic goals to reduce the risk or slow the progression of diabetic retinopathy. **A**

12.2 Implement strategies to help people with diabetes reach blood pressure and lipid goals to reduce the risk or slow the progression of diabetic retinopathy. **A**

Diabetic retinopathy is a highly specific neurovascular complication of both type 1 and type 2 diabetes, with prevalence strongly related to both the duration of diabetes and the level of glycemic management (1). Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years in developed countries. Glaucoma, cataracts, and other eye disorders occur earlier and more frequently in people with diabetes.

In addition to diabetes duration, factors that increase the risk of, or are associated with, retinopathy include chronic hyperglycemia (2,3), nephropathy (4), hypertension (5), and dyslipidemia (6–8). Intensive diabetes management with the goal of achieving near-normoglycemia has been shown in large prospective randomized studies to prevent and/or delay the onset and progression of diabetic retinopathy, reduce the need for future ocular surgical procedures, and potentially improve self-reported visual function (2,6,9–11). A meta-analysis of data from cardiovascular outcomes studies showed no association between glucagon-like peptide 1 receptor agonist (GLP-1 RA) treatment and retinopathy per se, except through the association between retinopathy and average A1C reduction at the 3-month and 1-year follow-up. Long-term impact of improved glycemic management on retinopathy was not studied in these trials. However, GLP-1 RAs including liraglutide, semaglutide, and dulaglutide have been shown to be

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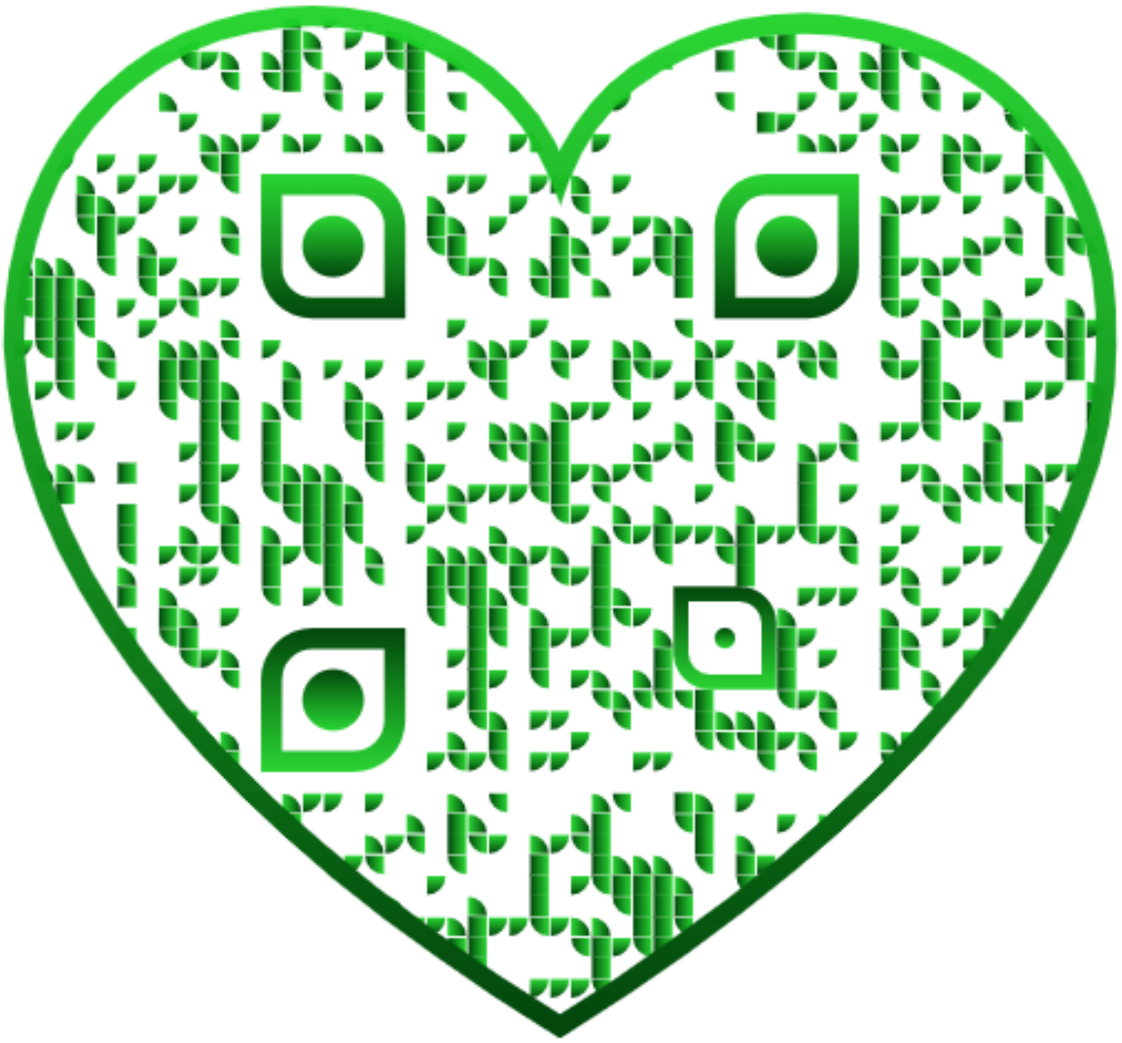

associated with a risk of mildly worsening diabetic retinopathy in randomized trials (12,13). Further data from clinical studies with longer follow-up purposefully designed for diabetic retinopathy risk assessment, particularly including individuals with established diabetic retinopathy, are needed. Retinopathy status should be assessed when glucose-lowering therapies are intensified, such as those using GLP-1 RAs, since rapid reductions in A1C can be associated with initial worsening of retinopathy (14).

Screening

Recommendations

12.3 Adults with type 1 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist within 5 years after the onset of diabetes. **B**

12.4 People with type 2 diabetes should have an initial dilated and comprehensive eye examination by an ophthalmologist or optometrist at the time of the diabetes diagnosis. **B**

12.5 If there is no evidence of retinopathy from one or more annual eye exams and glycemic indicators are within the goal range, then screening every 1–2 years may be considered. If any level of diabetic retinopathy is present, subsequent dilated retinal examinations should be repeated at least annually by an ophthalmologist or optometrist. If retinopathy is progressing or sight-threatening, then examinations by an ophthalmologist will be required more frequently. **B**

12.6 Programs that use retinal photography with remote reading or the use of U.S. Food and Drug Administration–approved artificial intelligence algorithms to improve access to diabetic retinopathy screening are appropriate screening strategies for diabetic retinopathy. Such programs need to provide pathways for timely referral for a comprehensive eye examination when indicated. **B**

12.7 Counsel individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who are pregnant on the risk of development and/or progression of diabetic retinopathy. **B**

12.8 Individuals with preexisting type 1 or type 2 diabetes should receive an eye exam before pregnancy as well as in the first trimester and may need to be monitored every trimester and for 1 year postpartum as indicated by the degree of retinopathy. **B**

Identifying individuals with diabetes-related eye disease is important because people with vision-threatening retinopathy may be asymptomatic. Additionally, current therapies can not only prevent vision loss but also help improve vision for many individuals. Prompt diagnosis allows triage of people with diabetes and timely intervention that may prevent vision loss in individuals who are asymptomatic despite advanced diabetes-related eye disease.

Diabetic retinopathy screening should be performed using validated approaches and methodologies. Youth with type 1 or type 2 diabetes are also at risk for complications and need to be screened for diabetic retinopathy (15–17) (see Section 14, "Children and Adolescents"). If diabetic retinopathy is evident on screening, prompt referral to an ophthalmologist is recommended. Subsequent examinations for individuals with type 1 or type 2 diabetes are generally repeated annually for individuals without or with mild retinopathy. Exams every 1–2 years may be cost-effective after one or more normal eye exams. In a population with well-managed type 2 diabetes, there was little risk of development of significant retinopathy within a 3-year interval after a normal examination (18), and less frequent intervals have been found in simulated modeling to be potentially effective in screening for diabetic retinopathy in individuals without diabetic retinopathy (19). However, it is important to adjust screening intervals based on the presence of specific risk factors for retinopathy onset and worsening retinopathy. More frequent examinations by the ophthalmologist will be required if retinopathy is progressing or risk factors such as not meeting glycemic goals, advanced retinopathy, or diabetic macular edema are present.

Retinal photography with remote reading by experts has great potential to provide screening services in areas where qualified eye care professionals are not readily available (20–22). High-quality fundus photographs can detect most clinically significant diabetic retinopathy. Interpretation of the images should be performed by a trained eye care professional or reading center technician or by artificial intelligence (AI) programs that are U.S. Food and Drug Administration (FDA) approved for this purpose. Retinal photography may also enhance efficiency and reduce costs when the expertise of ophthalmologists can be used for more complex examinations and for treatment (20,23,24). In-person exams are still necessary when the retinal photos are of unacceptable quality and for follow-up if abnormalities are detected. Retinal photos are not a substitute for dilated comprehensive eye exams, which should be performed at least initially and at yearly intervals thereafter or more frequently as recommended by an eye care professional. AI systems that detect more than mild diabetic retinopathy and diabetic macular edema that have been authorized for use by the FDA represent an alternative to traditional screening approaches (25). Three AI platforms have been approved by the FDA for diabetic retinopathy screening and examination: AEYE diagnostic screening technology, or AEYE-DS (AEYE Health); EyeArt AI screening system (Eyenuk); and LumineticsCore, formerly IDx-DR (Digital Diagnostics). These services are covered by most insurance plans. Prospective multicenter clinical trials on diagnostic accuracy have been published for each platform (26). However, the benefits and optimal utilization of this type of screening have yet to be fully determined. Results of all screening eye examinations should be documented and transmitted to the referring health care professional.

Type 1 Diabetes

Because retinopathy is estimated to take at least 5 years to develop after the onset of hyperglycemia, people with type 1 diabetes should have an initial dilated and comprehensive eye examination within 5 years after the diagnosis of diabetes (19).

Type 2 Diabetes

People with type 2 diabetes who may have had undiagnosed diabetes for years and have a significant risk of prevalent diabetic retinopathy at the time of diagnosis should have an initial dilated and comprehensive eye examination at the time of diagnosis.

Pregnancy

Individuals who develop gestational diabetes mellitus do not require eye examinations

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during pregnancy, since they do not appear to be at increased risk of developing diabetic retinopathy during pregnancy (27). However, individuals of childbearing potential with preexisting type 1 or type 2 diabetes who are planning pregnancy or who have become pregnant should be counseled on the baseline prevalence and risk of development and/or progression of diabetic retinopathy. In a systematic review and meta-analysis of 18 observational studies of pregnant individuals with preexisting type 1 or type 2 diabetes, the prevalence of any diabetic retinopathy and proliferative diabetic retinopathy (PDR) in early pregnancy was 52.3% and 6.1%, respectively. The pooled progression rate per 100 pregnancies for new diabetic retinopathy development was 15.0 (95% CI 9.9–20.8), worsened nonproliferative diabetic retinopathy was 31.0 (95% CI 23.2–39.2), pooled sight-threatening progression rate from nonproliferative diabetic retinopathy to PDR was 6.3 (95% CI 3.3–10.0), and worsened PDR was 37.0 (95% CI 21.2–54.0), demonstrating that close follow-up should be maintained during pregnancy to prevent vision loss (28). In addition, rapid implementation of intensive glycemic management in the setting of retinopathy is associated with early worsening of retinopathy, and these individuals may also benefit from more frequent follow-up initially (29).

A systematic review and meta-analysis and a controlled prospective study demonstrate that pregnancy in individuals with type 1 diabetes may aggravate retinopathy and threaten vision, especially when glycemic management is suboptimal or retinopathy severity is advanced at the time of conception (28,29). Laser photocoagulation surgery can minimize the risk of vision loss during pregnancy for individuals with high-risk PDR or center-involved diabetic macular edema (29). The use of anti–vascular endothelial growth factor (anti-VEGF) injections in pregnant individuals may be justified only if the potential benefit outweighs the potential risk to the fetus and only if clearly indicated. Current anti-VEGF medications have been assigned to pregnancy category C by the FDA (animal studies have revealed evidence of embryo-fetal toxicity, but there are no controlled data in human pregnancy), and caution should be used in pregnant individuals with diabetes because of theoretical risks to the vasculature of the developing fetus.

Treatment

Recommendations

12.9 Promptly refer individuals with any level of diabetic macular edema, moderate or worse nonproliferative diabetic retinopathy (a precursor of proliferative diabetic retinopathy [PDR]), or any PDR to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy. **A**

12.10 Panretinal laser photocoagulation therapy is indicated to reduce the risk of vision loss in individuals with high-risk PDR and, in some cases, severe nonproliferative diabetic retinopathy. **A**

12.11 Intravitreous injections of anti–vascular endothelial growth factor (anti-VEGF) are a reasonable alternative to traditional panretinal laser photocoagulation for some individuals with PDR and also reduce the risk of vision loss in these individuals. **A**

12.12 Intravitreous injections of anti-VEGF are indicated as first-line treatment for most eyes with diabetic macular edema that involves the foveal center and impairs vision acuity. **A**

12.13 Macular focal/grid photocoagulation and intravitreal injections of corticosteroid are reasonable treatments in eyes with persistent diabetic macular edema despite previous anti-VEGF therapy or eyes that are not candidates for this first-line approach. **A**

12.14 The presence of retinopathy is not a contraindication to aspirin therapy for cardioprotection, as aspirin does not increase the risk of retinal hemorrhage. **A**

Two of the main motivations for screening for diabetic retinopathy are to prevent loss of vision and to intervene with treatment when vision loss can be prevented or reversed.

Photocoagulation Surgery

Two large trials, the Diabetic Retinopathy Study (DRS) in individuals with PDR and the Early Treatment Diabetic Retinopathy Study (ETDRS) in individuals with macular edema, provide the strongest support for the therapeutic benefits of laser photocoagulation surgery. The DRS (30) showed that panretinal photocoagulation surgery reduced the risk of severe vision loss from PDR from 15.9% in untreated eyes to 6.4% in treated eyes with the greatest benefit ratio in those with more advanced baseline disease (disc neovascularization or vitreous hemorrhage). Later, the ETDRS verified the benefits of panretinal photocoagulation for high-risk PDR and in older-onset individuals with severe nonproliferative diabetic retinopathy or less-than-high-risk PDR (31). Panretinal laser photocoagulation is still commonly used to manage proliferative diabetic retinopathy. A macular focal/grid laser photocoagulation technique was shown in the ETDRS to be effective in treating eyes with clinically significant macular edema from diabetes (31), but this is now largely considered a second-line treatment for diabetic macular edema.

Anti-VEGF Treatment

Data from the DRCR Retina Network (formerly the Diabetic Retinopathy Clinical Research Network) and others demonstrate that intravitreal injections of anti-VEGF agents are effective at regressing proliferative disease and lead to noninferior or superior visual acuity outcomes compared with panretinal laser over 2 years of follow-up (32,33). In addition, it was observed that individuals treated with ranibizumab tended to have less peripheral visual field loss, fewer vitrectomy surgeries for secondary complications from their proliferative disease, and a lower risk of developing diabetic macular edema (32). However, a potential drawback in using anti-VEGF therapy to manage proliferative disease is that individuals were required to have a greater number of visits and received a greater number of treatments than is typically required for management by panretinal laser, which may not be optimal for some individuals. Additionally, unlike panretinal laser, anti-VEGF therapy requires participation in scheduled follow-up. Individuals with nonintentional lapses in treatment are at risk for worse visual acuity and anatomic outcomes (34). The FDA has approved aflibercept and ranibizumab for the treatment of eyes with diabetic retinopathy. Other emerging therapies for retinopathy that may use sustained intravitreal delivery of pharmacologic agents are currently under investigation. Anti-VEGF treatment of eyes with nonproliferative diabetic retinopathy has been demonstrated to reduce subsequent development of retinal neovascularization and diabetic macular edema

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but has not been shown to improve visual outcomes over 2 years of therapy and therefore has not been widely adopted for this indication (35).

While the ETDRS (31) established the benefit of focal laser photocoagulation surgery in eyes with clinically significant macular edema (defined as retinal edema located at or threatening the macular center), current data from well-designed clinical trials demonstrate that intravitreal anti-VEGF agents provide more effective treatment for center-involved diabetic macular edema than monotherapy with laser (36,37). With ranibizumab and aflibercept, most individuals require administration of intravitreal therapy with anti-VEGF agents every 4–8 weeks during the first 12 months of treatment, with fewer injections needed in subsequent years to maintain remission from center-involved diabetic macular edema. Five anti-VEGF agents currently are used to treat eyes with center-involved diabetic macular edema, namely, bevacizumab, ranibizumab, aflibercept (2 mg and 8 mg), brolucizumab, and faricimab (1), and a comparative effectiveness study demonstrated that aflibercept provides vision outcomes superior to those of bevacizumab when eyes have moderate visual impairment (vision of 20/50 or worse) from diabetic macular edema (38). For eyes that have good vision (20/25 or better) despite diabetic macular edema, close monitoring with initiation of anti-VEGF therapy if vision worsens provides 2-year vision outcomes similar to those of immediate initiation of anti-VEGF therapy (39).

Eyes that have persistent diabetic macular edema despite anti-VEGF treatment may benefit from macular laser photocoagulation or intravitreal therapy with corticosteroids (40). Both of these therapies are also reasonable first-line approaches for individuals who are not candidates for anti-VEGF treatment due to systemic considerations such as pregnancy.

Adjunctive Therapy

Lowering blood pressure has been shown to decrease retinopathy progression, although strict goals (systolic blood pressure <120 mmHg) do not impart additional benefit (6). In individuals with dyslipidemia, retinopathy progression may be slowed by the addition of fenofibrate, particularly with early diabetic retinopathy at baseline (41–43). Several studies have shown an association with GLP-1 RA and lower intraocular pressure (44) as well as a reduced risk of glaucoma (45–47).

Visual Rehabilitation

Recommendations

12.15 People who experience vision loss from diabetes should be counseled on the availability and scope of vision rehabilitation care and provided, or referred for, a comprehensive evaluation of their visual impairment by a practitioner experienced in vision rehabilitation. **E**

12.16 People with vision loss from diabetes should receive educational materials and resources for eye care support in addition to self-management education (e.g., glycemic management and hypoglycemia awareness). **E**

In the U.S., ~12% of adults with diabetes have some level of vision impairment (48). They may have difficulty reaching their diabetes treatment goals and performing many other activities of daily living, which can lead to depression, anxiety, social isolation, and difficulties at home, in the workplace, or at school (49).

People with diabetes are at increased risk of chronic vision loss, subsequent functional decline, and resulting disability. Vision impairment has physical, psychological, behavioral, and social consequences that affect people with diabetes, their families, friends, and caregivers. Health care professionals and stakeholders may not be aware of the overall impact of vision loss on an individual's health and well-being. People with diabetic vision loss should be evaluated to determine their potential to benefit from comprehensive vision restoration. Vision rehabilitation can help people with vision loss achieve maximum function, independence, and quality of life.

NEUROPATHY

Screening

Recommendations

12.17 All people with diabetes should be assessed for diabetic peripheral neuropathy starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes and at least annually thereafter. **B**

12.18 Assessment for distal symmetric polyneuropathy should include a careful history and assessment of either temperature or pinprick sensation (small-fiber function) and vibration sensation using a 128-Hz tuning fork (for large-fiber function). All people with diabetes should have annual 10-g monofilament testing to identify feet at risk for ulceration and amputation. **B**

12.19 Symptoms and signs of autonomic neuropathy should be assessed in people with diabetes starting at diagnosis of type 2 diabetes and 5 years after the diagnosis of type 1 diabetes, and at least annually thereafter, and with evidence of other microvascular complications, particularly kidney disease and diabetic peripheral neuropathy. Screening can include asking about orthostatic dizziness, syncope, early satiety, erectile dysfunction, changes in sweating patterns, or dry cracked skin in the extremities. Signs of autonomic neuropathy include orthostatic hypotension, a resting tachycardia, or evidence of peripheral dryness or cracking of skin. **E**

Diabetic neuropathies are a heterogeneous group of disorders with diverse clinical manifestations. The early recognition and appropriate management of neuropathy in people with diabetes is important. Points to be aware of include the following:

1. Diabetic neuropathy is a diagnosis of exclusion. Non–diabetic neuropathies may be present in people with diabetes and may be treatable.
2. Up to 50% of diabetic peripheral neuropathy may be asymptomatic. If not recognized and if preventive foot care is not implemented, people with diabetes are at risk for injuries as well as diabetic foot ulcers (DFUs) and amputations.
3. Recognition and treatment of autonomic neuropathy may improve symptoms, reduce sequelae, and improve quality of life.

Specific treatment to reverse the underlying nerve damage is currently not available. Glycemic management can effectively prevent diabetic peripheral neuropathy (DPN) and cardiovascular autonomic neuropathy (CAN) in type 1 diabetes (50,51) and may modestly slow their progression in type 2 diabetes (52), but it does not

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reverse neuronal loss. Treatments of other modifiable risk factors (including obesity, lipids, and blood pressure) can aid in prevention of DPN progression in type 2 diabetes and may reduce disease progression in type 1 diabetes (53–56). Therapeutic strategies (pharmacologic and nonpharmacologic) for the relief of painful DPN and symptoms of autonomic neuropathy can potentially reduce pain (57) and improve quality of life.

Diagnosis

Diabetic Peripheral Neuropathy

Individuals with a type 1 diabetes duration ≥5 years and all individuals with type 2 diabetes should be assessed annually for DPN using medical history and simple clinical tests (57). Symptoms vary according to the class of sensory fibers involved. The most common early symptoms are induced by the involvement of small fibers and include pain and dysesthesia (unpleasant sensations of burning and tingling). The involvement of large fibers may cause balance issues, numbness, and loss of protective sensation (LOPS). LOPS indicates the presence of distal sensory polyneuropathy and is a risk factor for diabetic foot ulceration. The following clinical tests may be used to assess small- and large-fiber function and protective sensation:

1. Small-fiber function: pinprick and temperature sensation.
2. Large-fiber function: lower-extremity reflexes, vibration perception, and 10-g monofilament.
3. Protective sensation: 10-g monofilament.

These tests not only screen for the presence of dysfunction but also predict future risk of complications. Electrophysiological testing or referral to a neurologist is rarely needed, except in situations where the clinical features are atypical (acute or subacute presentation, non–length dependent, asymmetric, and/or motor involvement) or the diagnosis is unclear.

In all people with diabetes and DPN, causes of neuropathy other than diabetes should be considered, including toxins (e.g., alcohol), neurotoxic medications (e.g., chemotherapy), vitamin B12 deficiency, hypothyroidism, kidney disease, malignancies (e.g., multiple myeloma, bronchogenic carcinoma), infections (e.g., HIV), chronic inflammatory demyelinating neuropathy, inherited neuropathies, and vasculitis (58). See the American Diabetes Association position statement "Diabetic Neuropathy" for more details (57).

Diabetic Autonomic Neuropathy

Individuals who have had type 1 diabetes for ≥5 years and all individuals with type 2 diabetes should be assessed annually for autonomic neuropathy (57). The symptoms and signs of autonomic neuropathy should be elicited carefully during the history and physical examination. Major clinical manifestations of diabetic autonomic neuropathy include resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and sudomotor dysfunction with either increased or decreased sweating. Screening for symptoms of autonomic neuropathy includes asking about symptoms of orthostatic intolerance (dizziness, lightheadedness, or weakness with standing), syncope, exercise intolerance, constipation, diarrhea, urinary retention, urinary incontinence, or changes in sweat function. Further testing can be considered if symptoms are present and will depend on the end organ involved but might include cardiovascular autonomic testing, sweat testing, urodynamic studies, gastric emptying, or endoscopy or colonoscopy. Impaired counterregulatory responses to hypoglycemia in type 1 and type 2 diabetes can lead to impaired hypoglycemia awareness but are not directly linked to autonomic neuropathy.

Cardiovascular Autonomic Neuropathy

CAN is associated with mortality independent of other cardiovascular risk factors (59,60). In its early stages, CAN may be completely asymptomatic and detected only by decreased heart rate variability with deep breathing. Advanced disease may be associated with resting tachycardia (>100 bpm) and orthostatic hypotension (a fall in systolic or diastolic blood pressure by >20 mmHg or >10 mmHg, respectively, upon standing without an appropriate increase in heart rate). CAN treatment is generally focused on alleviating symptoms.

Gastrointestinal Neuropathies

Gastrointestinal neuropathies may involve any portion of the gastrointestinal tract, with manifestations including esophageal dysmotility, gastroparesis, constipation, diarrhea, and fecal incontinence. Gastroparesis should be suspected in individuals with erratic glycemic management or with upper gastrointestinal symptoms without another identified cause. Exclusion of reversible/iatrogenic causes such as medications or organic causes of gastric outlet obstruction or peptic ulcer disease (with esophagogastroduodenoscopy or a barium study of the stomach) is needed before considering a diagnosis of or specialized testing for gastroparesis. The diagnostic gold standard for gastroparesis is the measurement of gastric emptying with scintigraphy of digestible solids at 15-min intervals for 4 h after food intake. The use of ^{13}C octanoic acid breath test is an approved alternative.

Genitourinary Disturbances

Diabetic autonomic neuropathy may also cause genitourinary disturbances, including sexual dysfunction and bladder dysfunction. In men, diabetic autonomic neuropathy may cause erectile dysfunction and/or retrograde ejaculation (57). Female sexual dysfunction occurs more frequently in those with diabetes and presents as decreased sexual desire, increased pain during intercourse, decreased sexual arousal, and inadequate lubrication (61). Lower urinary tract symptoms manifest as urinary incontinence and bladder dysfunction (nocturia, frequent urination, urination urgency, and weak urinary stream). Evaluation of bladder function should be performed for individuals with diabetes who have recurrent urinary tract infections, pyelonephritis, incontinence, or a palpable bladder.

Treatment

Recommendations

12.20 Optimize glucose management to prevent or delay the development of neuropathy in people with type 1 diabetes **A** and to slow the progression of neuropathy in people with type 2 diabetes. **C** Optimize weight, blood pressure, and serum lipid management to reduce the risk or slow the progression of diabetic neuropathy. **B**

12.21 Assess and treat pain related to diabetic peripheral neuropathy **B** and symptoms of autonomic neuropathy to improve quality of life. **E**

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12.22 Gabapentinoids, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants, and sodium channel blockers are recommended as initial pharmacologic treatments for neuropathic pain in diabetes. **A** Opioids, including tramadol and tapentadol, should not be used for neuropathic pain treatment in diabetes given the potential for adverse events. **B**

Glycemic Management

Near-normal glycemic management, implemented early in the course of diabetes, has been shown to effectively delay or prevent the development of DPN and CAN in people with type 1 diabetes (62–65). Although the evidence for the benefit of near-normal glycemic management is not as strong for type 2 diabetes, some studies have demonstrated a modest slowing of progression without reversal of neuronal loss (52,66). Specific glucose-lowering strategies may have different effects. In a post hoc analysis, participants, particularly men, in the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) trial treated with insulin sensitizers had a lower incidence of distal symmetric polyneuropathy over 4 years than those treated with insulin or sulfonylurea (67). Additionally, recent evidence from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial showed benefit of intensive glucose and blood pressure management on the prevention of CAN in type 2 diabetes (68).

Weight Management

Obesity is consistently associated with neuropathy in cross-sectional and longitudinal studies (69). While obesity has been established as a risk factor for neuropathy, including in those with diabetes, treatments of obesity are less well studied. The Look AHEAD (Action for Health in Diabetes) randomized trial found that a lifestyle intervention primarily focused on dietary weight loss led to improvements in neuropathy symptoms but not neuropathy examination scores (53). Observational studies of metabolic surgery have also revealed improvements in neuropathy outcomes, but randomized trials are lacking (55,56). Weight loss medications have not been well studied to date with two negative trials (topiramate and exenatide). Trials investigating the impacts of exenatide and topiramate on DPN and CAN measurements led to no substantial weight loss (70,71). Exercise often leads to a small reduction in weight and may also have positive effects on diabetic neuropathy through other mechanisms. Two systematic reviews have shown that exercise interventions improve diabetic neuropathy outcomes, including symptoms, examination findings, balance, and functional assessments, but the strength of the evidence is low (72,73).

Lipid Management

Dyslipidemia is a key factor in the development of neuropathy in people with type 2 diabetes and may contribute to neuropathy risk in people with type 1 diabetes (74,75). Although the evidence for a relationship between lipids and neuropathy development has become increasingly clear in type 2 diabetes, the optimal therapeutic intervention has not been identified. Positive effects of physical activity, weight loss, and metabolic surgery have been reported in individuals with DPN, but use of conventional lipid-lowering pharmacotherapy (such as statins or fenofibrates) does not appear to be effective in treating or preventing DPN development (76).

Blood Pressure Management

There are multiple reasons for blood pressure management in people with diabetes, and neuropathy progression (especially in type 2 diabetes) has now been added to this list. Although data from many studies have supported the role of hypertension in the risk of neuropathy development, a meta-analysis of data from 14 countries in the International Prevalence and Treatment of Diabetes and Depression (INTERPRET-DD) study revealed hypertension as an independent risk factor for DPN development with an odds ratio of 1.58 (95% CI 1.18–2.12) (77). In the ACCORD trial, intensive blood pressure intervention also decreased CAN risk by 25% (68).

Neuropathic Pain

Neuropathic pain can be severe and can impact quality of life, affect sleep, limit mobility, and contribute to depression and anxiety (78). No compelling evidence exists in support of glycemic or lifestyle management as therapies for neuropathic pain in diabetes or prediabetes, which leaves only pharmaceutical interventions (79). A recent guideline by the American Academy of Neurology recommends that the initial treatment of pain should also focus on the concurrent treatment of both sleep and mood disorders because of increased frequency of these problems in individuals with DPN (80).

Several pharmacologic therapies exist for treatment of pain in diabetes. The American Academy of Neurology (AAN) update suggested that gabapentinoids, serotonin-norepinephrine reuptake inhibitors (SNRIs), sodium channel blockers, and tricyclic antidepressants (TCAs) all could be considered in the treatment of pain in DPN (80). These AAN recommendations offer a supplement to a recent American Diabetes Association pain monograph (81). A head-to-head trial suggested therapeutic equivalency for TCAs, SNRIs, and gabapentinoids in the treatment of pain in DPN (82). The trial also supported the role of combination therapy over monotherapy for the treatment of pain in DPN.

Gabapentinoids. Gabapentinoids include several calcium channel $\alpha 2$-δ subunit ligands. Several high-quality and medium-quality studies support the role of pregabalin in treatment of pain in DPN. One high-quality study and many small studies support the role of gabapentin in the treatment of pain in DPN. Medium-quality studies suggest that mirogabalin has a small effect on pain in DPN (80). Adverse effects may be more severe in older individuals (83) and may be attenuated by lower starting doses and more gradual titration.

SNRIs. SNRIs include duloxetine, venlafaxine, and desvenlafaxine, all selective SNRIs. Two high-quality studies and five medium-quality studies support the role of duloxetine in the treatment of pain in DPN. A high-quality study supports the role of venlafaxine in the treatment of pain in DPN. Only one medium-quality study supports a possible role for desvenlafaxine for treatment of pain in DPN (80). Adverse events may be more severe in older people but may be attenuated with lower doses and slower titration of duloxetine.

Tricyclic Antidepressants. TCAs have been studied for treatment of pain. Most of the relevant data were acquired from trials of amitriptyline and include two high-quality studies and two medium-quality

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studies supporting the effectiveness of amitryiptylinein the treatment of painful DPN (80,82). Anticholinergic side effects may be dose limiting and restrict use in individuals ≥65 years of age.

Sodium Channel Blockers. Sodium channel blockers include lamotrigine, lacosamide, carbamazepine, oxcarbazepine, and valproic acid. Five medium-quality studies support the role of sodium channel blockers in treating pain in DPN (80).

Capsaicin. Capsaicin has received FDA approval for treatment of pain in DPN using an 8% patch, with one high-quality study reported. One medium-quality study of 0.075% capsaicin cream has been reported. In individuals with contraindications to oral pharmacotherapy or who prefer topical treatments, the use of topical capsaicin can be considered.

Lidocaine 5% Plaster/Patch. Lidocaine patches have limited data supporting their use in DPN and are not effective in more widespread distribution of pain (although they may be of use in individuals with nocturnal neuropathic foot pain). Lidocaine patches cannot be used for more than 12 h in a 24-h period (84).

Opioids. Several randomized controlled trials (RCTs) have demonstrated that opioids (dextromethorphan, oxycodone, morphine sulfate) can reduce pain in individuals with DPN (84). However, evidence for the long-term efficacy of opioids in neuropathic pain is lacking. In fact, the Centers for Disease Control and Prevention (CDC) performed a systematic review that found no studies of opioids for chronic pain have evaluated long-term outcomes, including pain, function, and quality of life (85). Moreover, CDC and AAN reviews have documented the long-term harms from opioids, including abuse, addiction, fractures, heart attacks, motor vehicle accidents, overdose, and mortality (85,86). The current evidence balancing risks and benefits has led the AAN to recommend against opioids for the treatment of painful DPN (80).

Tapentadol and Tramadol. Tapentadol and tramadol exert their analgesic effects through both μ-opioid receptor agonism (opioid) and norepinephrine and serotonin reuptake inhibition. Given that opioids and SNRIs are both effective for painful DPN, it is not surprising that these SNRI and opioid agents are effective in the treatment of pain in DPN too (80). However, the effect size is similar to that of other effective therapies, such as SNRIs, and these medications have the same risks as other opioids listed above. In fact, tramadol has been shown to be associated with all-cause mortality with an effect size similar to that of codeine (87). Similar to other opioids, risks likely outweigh benefits, and the AAN guidelines also recommend against their use for painful DPN (80).

Orthostatic Hypotension

Treating orthostatic hypotension is challenging. The therapeutic goal is to minimize postural symptoms rather than to restore normotension. Most individuals require both nonpharmacologic measures (e.g., ensuring adequate salt intake, avoiding medications that aggravate hypotension, or using compressive garments over the legs and abdomen) and pharmacologic measures. Physical activity and exercise should be encouraged to avoid deconditioning, which is known to exacerbate orthostatic intolerance, and volume repletion with fluids and salt is critical. Additionally, supine blood pressure tends to be much higher in these individuals, often requiring treatment of blood pressure at bedtime with shorter-acting drugs that also affect baroreceptor activity such as guanfacine or clonidine, shorter-acting calcium blockers (e.g., isradipine), or shorter-acting β-blockers such as atenolol or metoprolol tartrate. Alternatives can include enalapril if an individual is unable to tolerate preferred agents (88–90). Midodrine and droxidopa are approved by the FDA for the treatment of orthostatic hypotension.

Gastroparesis

Treatment of diabetic gastroparesis may be very challenging. A small-particle diet may provide some symptom relief (91–93). In addition, foods with small particle size may improve key symptoms (94). Withdrawing drugs with adverse effects on gastrointestinal motility, including opioids, anticholinergics, TCAs, GLP-1 RAs, and pramlintide, may also improve intestinal motility (91,95). However, the risk of removal of GLP-1 RAs should be balanced against their potential benefits. In cases of severe gastroparesis, pharmacologic interventions are needed. Only metoclopramide, a prokinetic agent, is approved by the FDA for the treatment of gastroparesis (96). However, the level of evidence regarding the benefits of metoclopramide for the management of gastroparesis is weak, and given the risk for serious adverse effects (extrapyramidal signs such as acute dystonic reactions, drug-induced parkinsonism, akathisia, and tardive dyskinesia), its use in the treatment of gastroparesis beyond 12 weeks is no longer recommended by the FDA. It should be reserved for severe cases that are unresponsive to other therapies (95). Other treatment options include domperidone (available outside the U.S.) and erythromycin, which is only effective for short-term use due to tachyphylaxis (96). Gastric electrical stimulation using a surgically implantable device has received approval from the FDA, although there are very limited data on DPN and the results do not support gastric stimulation as an effective therapy in diabetic gastroparesis (97).

Erectile Dysfunction

In addition to treatment of hypogonadism if present, treatments for erectile dysfunction may include phosphodiesterase type 5 inhibitors, intracorporeal or intraurethral prostaglandins, vacuum devices, or penile prostheses. As with DPN treatments, these interventions do not change the underlying pathology and natural history of the disease process but may improve a person's quality of life.

FOOT CARE

Recommendations

12.23 Perform a comprehensive foot evaluation at least annually to identify risk factors for ulcers and amputations. **A**

12.24 The examination should include inspection of the skin, assessment of foot deformities, neurological assessment (10-g monofilament testing or Ipswich touch test with at least one additional assessment: pinprick, temperature, or vibration), and vascular assessment, including pulses in the legs and feet. **B**

12.25 Individuals with evidence of sensory loss or prior ulceration or amputation should have their feet inspected at every visit. **A**

12.26 Obtain a prior history of ulceration, amputation, Charcot foot, angioplasty or vascular surgery, cigarette

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smoking, retinopathy, and renal disease and assess current symptoms of neuropathy (pain, burning, numbness) and vascular disease (leg fatigue, claudication). B

12.27 Initial screening for peripheral arterial disease (PAD) should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time. Individuals with a history of leg fatigue, claudication, and rest pain relieved with dependency or decreased or absent pedal pulses should be referred for ankle-brachial index with toe pressures and for further vascular assessment as appropriate. B

12.28 An interprofessional approach facilitated by a podiatrist in conjunction with other appropriate team members is recommended for individuals with foot ulcers and high-risk feet (e.g., those on dialysis, those with Charcot foot, those with a history of prior ulcers or amputation, and those with PAD). B

12.29 Refer individuals who smoke and have a history of prior lower-extremity complications, loss of protective sensation, structural abnormalities, or PAD to foot care specialists for ongoing preventive care and lifelong surveillance. B These individuals should also be provided with information on the importance of smoke cessation and referred for counseling on smoke cessation. A

12.30 Provide general preventive foot self-care education to all people with diabetes, including those with loss of protective sensation, on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems. B

12.31 The use of specialized therapeutic footwear is recommended for people with diabetes at high risk for ulceration, including those with loss of protective sensation, foot deformities, ulcers, callous formation, poor peripheral circulation, or history of amputation. B

12.32 For chronic diabetic foot ulcers that have failed to heal with optimal standard care alone, adjunctive treatment with randomized controlled trial–proven advanced agents should be considered. Considerations might include negative-pressure wound therapy, placental membranes, bioengineered skin substitutes, several acellular matrices, autologous fibrin and leukocyte platelet patches, and topical oxygen therapy. A

Foot ulcerations and amputations are common complications associated with diabetes. These may be the consequences of several factors, including peripheral neuropathy, PAD, and foot deformities. They represent major causes of morbidity and mortality in people with diabetes. Early recognition of at-risk feet, preulcerative lesions, and prompt treatment of ulcerations and other lower-extremity complications can delay or prevent adverse outcomes.

Early recognition requires an understanding of those factors that put people with diabetes at increased risk for ulcerations and amputations. Factors that are associated with the at-risk foot include the following:

- Poor glycemic management
- Peripheral neuropathy/LOPS
- PAD
- Foot deformities (bunions, hammertoes, Charcot joint, etc.)
- Preulcerative corns or calluses
- Prior ulceration
- Prior amputation
- Smoking
- Retinopathy
- Nephropathy (particularly individuals on dialysis or posttransplant)

Identifying the at-risk foot begins with a detailed history documenting diabetes management, smoking history, exercise tolerance, history of claudication or rest pain, and prior ulcerations or amputations. A thorough examination of the feet should be performed annually in all people with diabetes and more frequently in at-risk individuals (98). The examination should include assessment of skin integrity, assessment for LOPS using the 10-g monofilament along with at least one other neurological assessment tool, pulse examination of the dorsalis pedis and posterior tibial arteries, and assessment for foot deformities such as bunions, hammertoes, and prominent metatarsals, which increase plantar foot pressures and increase risk for ulcerations. At-risk individuals should be assessed at each visit and should be referred to foot care specialists for ongoing preventive care and surveillance. The physical examination can stratify people with diabetes into different categories and determine the frequency of these visits (99) (**Table 12.1**).

Evaluation for Loss of Protective Sensation

The presence of peripheral sensory neuropathy is the single most common component cause for foot ulceration. In a multicenter trial, peripheral neuropathy was found to be a component cause in 78% of people with diabetes with ulcerations and that the triad of peripheral sensory neuropathy, minor trauma, and foot deformity was present in >63% of participants (100). All people with diabetes should undergo a comprehensive foot examination at least annually or more frequently for those in higher-risk categories (98,99).

LOPS is vital to risk assessment. One of the most useful tests to determine LOPS is the 10-g monofilament test. Studies have shown that clinical examination and the 10-g monofilament test are the two most sensitive tests in identifying the foot at risk for ulceration (101). The monofilament test should be performed with at least one other neurologic assessment tool (e.g., pinprick, temperature perception, ankle reflexes, or vibratory perception with a 128-Hz tuning fork or similar device). Absent monofilament sensation and one other abnormal test confirms the presence of LOPS. Further neurological testing, such as nerve conduction, electromyography, nerve biopsy, or intraepidermal nerve fiber density biopsies, are rarely indicated for the diagnosis of peripheral sensory neuropathy (57).

Evaluation for Peripheral Arterial Disease

Initial screening for PAD should include a history of leg fatigue, claudication, and rest pain relieved with dependency. Physical examination for PAD should include assessment of lower-extremity pulses, capillary refill time, rubor on dependency, pallor on elevation, and venous filling time (98,102). Any individual exhibiting signs and symptoms of PAD should be referred for noninvasive arterial studies in the form of Doppler ultrasound with pulse volume recordings. While ankle-brachial indices will be calculated, they should be interpreted carefully, as they are known to be inaccurate in people

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Table 12.1—International Working Group on Diabetic Foot risk stratification system and corresponding foot screening frequency

Category	Ulcer risk	Characteristics	Examination frequency*
0	Very low	No LOPS and no PAD	Annually
1	Low	LOPS or PAD	Every 6–12 months
2	Moderate	LOPS + PAD, or LOPS + foot deformity, or PAD + foot deformity	Every 3–6 months
3	High	LOPS or PAD and one or more of the following: • History of foot ulcer • Amputation (minor or major) • End-stage renal disease	Every 1–3 months

Adapted with permission from Schaper et al. (99). LOPS, loss of protective sensation; PAD, peripheral artery disease. *Examination frequency suggestions are based on expert opinion and person-centered requirements.

with diabetes due to noncompressible vessels. Toe systolic blood pressure tends to be more accurate. Toe systolic blood pressure <30 mmHg is suggestive of PAD and an inability to heal foot ulcerations (103). Individuals with abnormal pulse volume recording tracings and toe pressures <30 mmHg with foot ulcers should be referred for immediate vascular evaluation. Due to the high prevalence of PAD in people with diabetes, the Society for Vascular Surgery and the American Podiatric Medical Association guidelines recommend that all people with diabetes >50 years of age should undergo screening via noninvasive arterial studies (102, 104). If normal, these should be repeated every 5 years (102).

Education for People With Diabetes

All people with diabetes (and their caregivers), particularly those with the aforementioned high-risk conditions, should receive general foot care education, including appropriate management strategies (105–107). This education should be provided to all newly diagnosed people with diabetes as part of an annual comprehensive examination and to individuals with high-risk conditions at every visit. Recent studies have shown that while education improves knowledge of diabetic foot problems and self-care of the foot, it does not improve behaviors associated with active participation in their overall diabetes care and the achievement of personal health goals (108). Evidence also suggests that while education for people with diabetes and their families is important, the knowledge is quickly forgotten and needs to be reinforced regularly (109).

Individuals considered at risk should understand the implications of foot deformities, LOPS, and PAD; the proper care of the foot, including nail and skin care; and the importance of daily foot inspections. Individuals with LOPS should be educated on appropriate ways to examine their feet (palpation or visual inspection with an unbreakable mirror) for daily surveillance of early foot problems. People with diabetes should also be educated on the importance of referrals to foot care specialists. A recent study showed that people with diabetes and foot disease lacked awareness of their risk status and why they were being referred to an interprofessional team of foot care specialists. Further, they exhibited a variable degree of interest in learning further about foot complications (110).

Individuals' understanding of these issues and their physical ability to conduct proper foot surveillance and care should be assessed. Those with visual difficulties, physical constraints preventing movement, or cognitive problems that impair their ability to assess the condition of the foot and to institute appropriate responses will need other people, such as family members, to assist with their care.

The selection of appropriate footwear and footwear behaviors at home should also be discussed (e.g., no walking barefoot, avoiding open-toed shoes). Therapeutic footwear with custom-made orthotic devices have been shown to reduce peak plantar pressures (107). Most studies use reduction in peak plantar pressures as an outcome as opposed to ulcer prevention. Certain design features of the orthoses, such as rocker soles and metatarsal accommodations, can reduce peak plantar pressures more significantly than insoles alone. A systematic review, however, showed there was no significant reduction in ulcer incidence after 18 months compared with standard insoles and extra-depth shoes. Further, it was also noted that evidence to prevent first ulcerations was nonexistent (111).

Treatment

Treatment recommendations for people with diabetes will be determined by their risk category. No-risk or low-risk individuals often can be managed with education and self-care. People in the moderate- to high-risk category should be referred to foot care specialists for further evaluation and regular surveillance as outlined in **Table 12.1**. This category includes individuals with LOPS, PAD, and/or structural foot deformities, such as Charcot foot, bunions, or hammertoes. Individuals with any open ulceration or unexplained swelling, erythema, or increased skin temperature should be referred urgently to a foot care specialist or interprofessional team.

Initial treatment recommendations should include daily foot inspection, use of moisturizers for dry, scaly skin, and avoidance of self-care of ingrown nails and calluses. Well-fitted athletic or walking shoes with customized pressure-relieving orthoses should be part of initial recommendations for people with increased plantar pressures (as demonstrated by plantar calluses). Individuals with deformities such as bunions or hammertoes may require specialized footwear such as extra-depth shoes. Those with even more significant deformities, as in Charcot joint disease, may require custom-made footwear. For recalcitrant deformities or for

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recurrent ulcerations not amenable to conservative footwear therapy alone, appropriate surgical reconstruction by an experienced diabetic foot surgeon should be considered (112,113).

Special consideration should be given to individuals with neuropathy who present with a warm, swollen, red foot with or without a history of trauma and without an open ulceration. These individuals require a thorough workup for possible Charcot neuroarthropathy (114,115). Foot and ankle X-rays should be performed in all individuals presenting with the above clinical findings. Early diagnosis and treatment of this condition is of paramount importance in preventing deformities and instability that can lead to ulceration and amputation. These individuals require total non–weight-bearing and urgent referral to a foot care specialist for further management. Surgical reconstruction of these complex limb-threatening deformities has assumed an important role in recent years, with many surgeries yielding high levels of success and limb salvage (113,116,117). Nonetheless, such procedures need to be approached by experienced surgeons with an appreciation not only for the complexities of the deformity but also for the complexities of the individuals themselves.

There have been a number of developments in the treatment of ulcerations over the years (118). These include negative-pressure therapy, growth factors, bioengineered tissue, acellular matrix tissue, stem cell therapy, hyperbaric oxygen therapy, and, most recently, topical oxygen therapy (119–121). While there is literature to support many modalities currently used to treat diabetic foot wounds, robust RCTs are often lacking. However, it is agreed that the initial treatment and evaluation of ulcerations include the following five basic principles of ulcer treatment:

- Offloading of plantar ulcerations
- Debridement of necrotic, nonviable tissue
- Revascularization of ischemic wounds when necessary
- Management of infection: soft tissue or bone
- Use of physiologic, topical dressings

However, despite following the above principles, some ulcerations will become chronic and fail to heal. Careful evaluation is necessary to determine if there are associated deformities predisposing to high plantar pressures that need to be addressed with surgical offloading procedures to expedite healing (112,122,123). Additionally, underlying osteomyelitis must be ruled out as a cause for the nonhealing ulcer and treated as necessary. Once these complicating factors have been addressed, adjunctive advanced wound therapy can play an important role. When to use advanced wound therapy has been the subject of much discussion, as the therapy is often quite expensive. It has been determined that if a wound fails to show a reduction of 50% or more after 4 weeks of appropriate wound management (i.e., the five basic principles above), consideration should be given to the use of advanced wound therapy (124). Treatment of these chronic wounds is best managed in an interprofessional setting.

Evidence to support advanced wound therapy is challenging to produce and to assess. Randomization of trial participants is difficult, as there are many variables that can affect wound healing. In addition, many RCTs exclude certain cohorts of people, e.g., individuals with chronic renal disease or those on dialysis. Finally, blinding of participants and clinicians is not always possible. Meta-analyses and systematic reviews of observational studies are used to determine the clinical effectiveness of these modalities. Such studies can augment formal RCTs by including a greater variety of participants in various clinical settings who are typically excluded from the more rigidly structured clinical trials.

Advanced wound therapy can be classified into nine broad categories (118) (**Table 12.2**). Topical growth factors, acellular matrix tissues, and bioengineered cellular therapies are commonly used in offices and wound care centers to expedite healing of chronic, more superficial ulcerations. Numerous clinical reports and retrospective studies have demonstrated the clinical effectiveness of each of these modalities. Over the years, there has been increased evidence to support the use of these modalities. Nonetheless, use of those products or agents with robust RCTs or systematic reviews should generally be preferred over those without level 1 evidence (**Table 12.2**).

Negative-pressure wound therapy was first introduced in the early to mid-1990s. It has become especially useful in wound preparation for skin grafts and flaps and assists in the closure of deep, large wounds (125,126). A variety of types exist in the marketplace and range from electrically powered to mechanically powered in different sizes depending upon the specific wound requirements.

Electrical stimulation, pulsed radiofrequency energy, and extracorporeal shockwave therapy are biophysical modalities that are believed to upregulate growth factors or cytokines to stimulate wound healing, while low-frequency noncontact ultrasound is used to debride wounds. However, most of the studies advocating the use of these modalities have been retrospective observational studies or poor-quality RCTs.

Hyperbaric oxygen therapy is the delivery of oxygen through a chamber, either individual or multiperson, with the intention of increasing tissue oxygenation to increase tissue perfusion and neovascularization, combat resistant bacteria, and stimulate wound healing. While there had been great interest in this modality being able to expedite healing of chronic diabetic foot ulcers (DFUs), there is one RCT with positive results that reported increased healing rates at 9 and 12 months compared with control participants (127). More recent studies with significant design deficiencies and participant dropouts have failed to provide corroborating evidence that hyperbaric oxygen therapy should be widely used for managing nonhealing DFUs (128,129). While there may be some benefit in prevention of amputation in selected chronic neuroischemic ulcers, recent studies have shown no benefit in healing DFUs in the absence of ischemia and/or infection (120,130).

Topical oxygen therapy has been studied rather vigorously in recent years, with several high-quality RCTs and at least five systematic reviews and meta-analyses all supporting its efficacy in healing chronic DFUs at 12 weeks (119,121,131–135). Three types of topical oxygen devices are available, including continuous-delivery, low-constant-pressure, and cyclical-pressure modalities. Importantly, topical oxygen therapy devices provide for home-based therapy and replace the need for daily visits to specialized centers. Very high participation with very few reported adverse events combined with improved healing rates makes this therapy another attractive option for advanced wound care.

If DFUs fail to heal despite appropriate standard or surgical wound care, adjunctive

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Table 12.2—Categories of advanced wound therapies

Negative-pressure wound therapy
Standard electrically powered
Mechanically powered
Oxygen therapies
Hyperbaric oxygen therapy
Topical oxygen therapy
Oxygen-releasing sprays, dressings
Biophysical
Electrical stimulation, diathermy
Pulsed electromagnetic fields, pulsed radiofrequency energy
Low-frequency noncontact ultrasound
Extracorporeal shock wave therapy
Growth factors
Becaplermin: platelet-derived growth factor
Fibroblast growth factor
Epidermal growth factor
Autologous blood products
Platelet-rich plasma
Leukocyte, platelet, fibrin multilayered patches
Whole blood clot
Acellular matrix tissues
Xenograft dermis
Bovine dermis
Xenograft acellular matrices
Small intestine submucosa
Porcine urinary bladder matrix
Ovine forestomach
Equine pericardium
Fish skin graft
Bovine collagen
Bilayered dermal regeneration matrix
Human dermis products
Human pericardium
Placental tissues
Amniotic tissues/amniotic fluid
Umbilical cord
Bioengineered allogeneic cellular therapies
Bilayered skin equivalent (human keratinocytes and fibroblasts)
Dermal replacement therapy (human fibroblasts)
Stem cell therapies
Autogenous: bone marrow–derived stem cells
Allogeneic: amniotic matrix with mesenchymal stem cells
Miscellaneous active dressings
Hyaluronic acid, honey dressings, etc.
Sucrose octasulfate dressing

Adapted with permission from Frykberg and Banks (118).

advanced therapies should be instituted and are best managed in an interprofessional manner. Once healed, all individuals should be enrolled in a formal comprehensive prevention program focused on reducing the incidence of recurrent ulcerations and subsequent amputations (98,136,137).

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